International Journal of Cardiology 293 (2019) 1–9

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Women with coronary microvascular dysfunction and no obstructive coronary artery disease have reduced exercise capacity☆,☆☆

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ARTICLE INFO

Article history:
Received 14 May 2019
Received in revised form 20 June 2019
Accepted 15 July 2019
Available online 17 July 2019

ABSTRACT

Background: Both coronary microvascular dysfunction (CMD) and reduced exercise capacity are associated with adverse cardiovascular prognosis. The association between CMD and cardiopulmonary exercise testing (CPET) derived exercise capacity in symptomatic individuals without obstructive coronary artery disease (CAD) is not clear. We investigated whether exercise capacity was reduced in women with angina, CMD and no obstructive CAD compared with sex-matched controls. Furthermore, we assessed the association between CMD and other CPET-derived variables.

Methods: All participants underwent transthoracic Doppler echocardiography of the left anterior descending artery with dipyridamole-induced vasodilation and CPET using ergometer cycle with an incremental test protocol.

Results: We included 99 women with angina and no obstructive CAD (patients) and 27 asymptomatic women (controls), age (mean ± standard deviation) 61 ± 10 and 58 ± 10 years, respectively. Patients had a higher burden of risk factors compared with controls, while the weekly physical activity level was comparable between the groups ($p = 0.72$). CMD was present in 27 (27%) patients and 5 (19%) controls. Peak VO_2 was significantly reduced in patients with CMD compared with controls with normal coronary microvascular function ((median (IQR) 17.3 (15.5–21.3) vs. 27.3 (21.6–30.8) ml/kg/min; age-adjusted $p = 0.001$), independent of cardiovascular risk factors ($p = 0.041$). Presence of CMD in symptomatic women was also associated with diminished heart rate reserve ($p < 0.001$) and blunted heart rate recovery.

Conclusions: Women with angina, CMD and no obstructive CAD have markedly reduced exercise capacity compared with sex-matched controls. Moreover, combination of angina and CMD is associated with impaired heart rate response and heart rate recovery.

1. Introduction

Many women presenting with chest pain suggestive of myocardial ischemia have no obstructive coronary artery disease (CAD) [1]. A mismatch between symptoms, clinical and angiography findings often results in a lack of diagnosis and limited treatment options. Furthermore, these patients are characterized by significant health services utilization, diminished quality of life, and increased cardiovascular morbidity and mortality [2–4]. Functional abnormality of coronary resistant vessels, including disruption of the endothelial dependent and/or non-endothelial dependent regulatory mechanisms, may cause coronary microvascular dysfunction (CMD), a mismatch between myocardial oxygen demand and blood supply [5]. CMD is the possible underlying cause of myocardial ischemia and adverse cardiovascular prognosis in some of these women [6].

Cardiopulmonary exercise testing (CPET) provides a safe, non-invasive evaluation of cardiac and circulatory functions in patients

Abbreviations: BMI, Body mass index; bpm, Beats per minute; CAD, Coronary artery disease; CFVR, Coronary flow velocity (CFV) reserve; CI, Chronotropic incompetence; CMD, Coronary microvascular dysfunction; CPET, Cardiopulmonary exercise testing; IPAQ, The International Physical Activity Questionnaire; iPOWER, ImProve diagnOsis and treatment of Women with angina pEctoris and micRovessel disease; HR, Heart rate; LV, Left ventricular; MET, Metabolic equivalent minutes; VO_2, Oxygen uptake; RER, Respiratory exchange ratio; TTDE, Transthoracic Doppler echocardiography.

☆ This manuscript, or any part of it, neither has been published nor is being considered for publication by any other journal. The authors report no conflict of interest. This work was supported by the Danish Heart Foundation (grant 11-10-R87-B-A3628-22678), Arvid Nilssons Foundation, and Hvidovre Hospital Research Council.

☆☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2019.07.048
0167-5273/

who are able to exercise [7]. Moreover, exercise capacity, quantified by oxygen consumption, is a significant predictor of cardiovascular disease and death in women [8]. Existing knowledge on exercise performance in symptomatic women without obstructive CAD is mostly limited to patients with cardiac syndrome X [9]. However, due to heterogeneity of the underlying pathophysiology, only some of these patients have CMD [10]. Earlier research has shown a positive association between peak oxygen uptake (peak VO_2; ml/kg/min) and coronary microvascular function in patients with heart failure or CAD [11–14]. The association between CMD and exercise capacity in symptomatic individuals without obstructive CAD is not clear.

The main purpose of this study was to investigate whether women with angina, CMD and no obstructive CAD have reduced exercise capacity compared with asymptomatic sex-matched controls. Also, we wished to explore the association between CMD and other CPET-derived variables.

2. Material and methods

2.1. Patient population

This is a substudy within the iPOWER (ImProve diagnOsis and treatment of Women with angina pEctoris and micRovessel disease), a Danish prospective observational multicenter study, aiming to investigate existing and novel techniques in diagnosis of CMD in women with angina and no obstructive CAD (<50% stenosis). Within the iPOWER cohort, we consecutively included women (18–80 years) with angina and no obstructive CAD on clinically indicated invasive coronary angiography, which constituted the patient population of this study. Angina was defined as typical, atypical or non-cardiac chest pain using existing criteria [15]. The main study design and the current sub-study in- and exclusion criteria are described elsewhere [16,17]. Briefly, we excluded women with chronic obstructive pulmonary disease, asthma, myocardial infarction or revascularization, peripheral arterial disease, reduced kidney function, elevated troponins, heart valve disease, cardiomyopathy, congenital heart disease, or left ventricle (LV) ejection fraction below 45%. Moreover, pregnant women, women unable to perform an exercise test, and participants with contra-indication to dipyridamole or theophylline were also excluded.

2.2. Control population

Asymptomatic women (18–80 years), with no history of angina, ischemic heart disease, and no significant CAD on coronary CT angiography (<50% stenosis), were randomly selected from the Copenhagen City Heart Study as a control population [17]. The same exclusion criteria applied for both patients and controls.

2.3. Basic examination

Demographics and medical history were collected from questionnaires and medical records and were cross checked during personal interviews conducted by trained health professionals. Hypertension, hypercholesterolemia, diabetes mellitus, smoking, and family history of ischemic heart disease were included as cardiovascular risk factors if they were stated in participant's medical records or if patient received appropriate medication. Self-reported weight and height were used to calculate body mass index (BMI). Physical activity level on weekly basis (metabolic equivalent minutes; MET- minutes per week) was assessed using the short version of The International Physical Activity Questionnaire (IPAQ). If a patient underwent a functional test (myocardial perfusion imaging and/or stress ECG) <6 months prior to the study inclusion, the result (positive/negative/inconclusive) was collected from the medical records.

2.4. CPET protocol and interpretation

CPET was conducted and interpreted according to the existing recommendations [7,18]. Prior to CPET, anti-hypertensive medications, beta-blockers, and medications containing short- or long-acting nitrates were paused for 24 h. Study participants were instructed to abstain from smoking and from intake of food 2 h prior to examination. Tests were performed using an upright Lode Corival® cycle ergometer (Lode Corival Ergometer, Groningen, The Netherlands). Jaeger MasterScreen® CPX software system (Cardinal health, *Würzburg*, Germany) was used for gas exchange and ventilatory measurements. The gas analyzer was calibrated before each test for barometric pressure, temperature, and humidity. A 12 lead ECG was monitored continuously, blood pressure was measured every second minute. Gas and ventilatory variables were measured continuously using a breath-to-breath method and averaged over 15 s intervals.

The exercise protocol consisted of 5 phases: rest (2 min), warm-up (3 min; work load 20 watt (W)), test (start at 25 W with 25 W increase every second minute), active recovery (3 min; work load 20 W), and passive recovery (3 min; no pedaling) [19]. Participants were instructed to keep the same pedaling speed (around 60 rounds/min) throughout the warm-up, test, and active recovery. Talking or standing during CPET was not allowed. All participants were encouraged to continue the test until physical exhaustion or discomfort. Participant's cardiovascular effort was assessed using peak respiratory exchange ratio (RER). Low peak RER during exercise in individuals without pulmonary disease may indicate submaximal effort, which may affect the estimation of peak VO_2. Therefore, CPET was considered successful when RER >1.1 was achieved [7]. For safety reasons, every test was performed by a medical doctor.

Peak VO_2 was defined as the highest average value of oxygen uptake during a 15 s interval indexed to body weight. To account for age differences, peak VO_2 was also reported as a percentage of predicted value using the equation for sedentary women by Wasserman and Hansen [7]. O_2 pulse was defined as the ratio of peak O_2 consumption (ml) to peak heart rate (HR; beats per minute [bpm]). $\Delta VO_2/\Delta$work rate was calculated as the rate of oxygen uptake as a function of work rate. Chronotropic responses were evaluated by HR reserve, calculated as the difference between peak HR during exercise and resting HR, in relation to predicted HR reserve, calculated as the difference between resting HR and the age-predicted peak HR (220-age) [7,20]. Heart rate recovery was defined as the change from peak HR to that measured 1 and 2 min into active recovery. HR recovery was calculated as the difference between peak HR and HR 1 min into active recovery. Ventilatory anaerobic threshold, defined as the level of oxygen uptake above which aerobic energy production is supplemented by anaerobic mechanisms, was automatically calculated by the software using the v-slope method [21]. Each v-plot was visually assessed for error measurements. Symptoms of chest discomfort and ECG abnormalities, including ST-segment changes, were documented throughout the test.

2.5. Echocardiography imaging protocol and interpretation

Prior to transthoracic echocardiography anti-hypertensive medications, beta-blockers, and short- or long-acting nitrates were paused for 24 h, and medications containing dipyridamole for 48 h. Study participants were instructed to abstain from smoking and from intake of food and drinks containing methylxanthines.

A detailed description of the imaging and interpretation protocols has been published elsewhere [22]. In brief, parameters of the LV diastolic function included pulsed-wave tissue Doppler velocities of the mitral annulus in early diastole in the lateral wall (e'), ratio between early (E) and late (A) peak velocities of the mitral inflow (E/A), mitral deceleration time (DT), and early transmitral velocity to *e'* ratio (*E*/e'). Parameters of the LV systolic function included LV ejection fraction (estimated using a semi-automated biplane Auto-EF tool) and cardiac output during rest and dipyridamole-induced hyperemia (0.84 mg/kg over 6 min).

The non-endothelial dependent aspect of the coronary microvascular function was evaluated non-invasively by transthoracic Doppler echocardiography (TTDE). TTDE was performed using a GE Healthcare Vivid E9 cardiovascular ultrasound system (GE Healthcare, Horten, Norway). Images were analysed using EchoPac software (GE EchoPac v.112, Norway) by an experienced reader blinded to patient data. Peak coronary flow velocities (CFV), measured in the proximal or mid left anterior descending artery during rest and hyperemia, were assessed in all participants using a 2.7–8 MHz transducer (GE Vivid 6S probe, GE Healthcare) [23]. CFV reserve (CFVR) was calculated as the ratio of peak diastolic CFV during hyperemia and peak resting CFV. CFVR <2 was considered to be a strong indicator of non-endothelial dependent CMD [1]. Good inter-observer variability and repeatability of CFVR by TTDE in both healthy young subjects and patients have previously been reported by our group [16,23].

3. Statistical analyses

Numerical variables are presented as mean ± standard deviation (SD) or median (interquartile range; IQR), depending on the data distribution. Categorical variables are presented as count (percentage). The study cohort consisted of women with angina (patients) and asymptomatic women (controls). The groups were further divided into women with and without CMD, and asymptomatic women with normal CFVR were used as the reference group when calculating *p*-values. Age-matching between patients and controls was prioritized during the enrollment but was not always feasible due to limited number of individuals who passed the in- and exclusion criteria and were willing to participate.

Linear regression analyses, Chi-square tests, two-sample *t*-tests and Wilcoxon rank sum tests were used to calculate intergroup differences in Tables 1–4. All intergroup comparisons, but age-adjusted predicted parameters, were adjusted for age. Reduced peak oxygen uptake (ml/min) has previously been associated with aging, obesity, and unfavorable cardiovascular risk profile [7,24–27]. Therefore, intergroup difference in peak VO_2 (ml/kg/min) between patients with CMD and the reference population was also assessed using multivariate regression analysis adjusted for age and risk factors (history of smoking, hypertension, hypercholesterolemia, and diabetes). BMI was omitted from the model because peak VO_2 already is adjusted for weight. Intergroup differences in HR reserve were adjusted for age, BMI, and risk factors (history of smoking, hypertension, hypercholesterolemia, and diabetes). All

calculations were performed using STATA software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

4. Ethics

This study was performed in accordance with the Helsinki Declaration and was approved by the Danish Regional Committee on Biomedical Research Ethics (H-3-2012-005). All study participants gave written informed consent after receiving oral and written information about the study.

5. Results

5.1. Study population

A total of 107 patients and 31 controls were enrolled. Eight patients were excluded due to incomplete CPET ($n = 1$) or submaximal effort (RER <1.1; $n = 7$). To achieve similar age distribution within the groups, the four youngest controls (age 31–39 years) were excluded, leaving 99 patients and 27 controls for the final analyses (mean ± SD age 61 ± 10 and 58 ± 10 years; $p = 0.22$). Analyses comparing peak VO_2 between patient and control groups, with the youngest controls included, yielded similar results to those presented here (Appendix, Table 3).

Patients were characterized by a higher burden of risk factors compared with controls (Table 1), while the weekly physical activity level was comparable between the groups ($p = 0.72$). CFVR was available for all controls and 98 patients (99%). CMD, defined as CFVR <2, was present in 27 (27%) patients and 5 (19%) controls ($p = 0.34$). Patients with CMD were older and had a higher prevalence of hypertension, hypercholesterolemia and smoking compared with controls with normal CFVR. Measured parameters of LV systolic and diastolic functions, but cardiac output at rest, were comparable between controls with normal CFVR and patients with CMD (Appendix, Table 4). Out of 99 patients included, 18 (18%) underwent a clinically indicated functional test prior to the study inclusion. Five (28%) tests were positive for ischemia, 6 (33%) were negative, and 7 (39%) were considered inconclusive (Table 1).

5.2. Peak oxygen uptake

All tests were terminated due to physical exhaustion. Exercise data for control and patient groups are outlined in Table 2. Four (4%) patients and no controls experienced chest discomfort without simultaneous ECG changes during the test period. Asymptomatic horizontal or downslope ST-depressions were registered in 7 (7%) patients and 1 (4%) control ($p = 0.43$). These did not result in early termination of the test and required no further follow-up.

Using asymptomatic women with normal CFVR as the reference group, fewer patients with CMD achieved the predicted peak VO_2 values (72% vs. 48%; $p = 0.037$; Appendix, Fig. 2a). Presence of CMD amongst controls was associated with a reduction in peak VO_2 (median (IQR) 24.2 (20.3–25.1) vs. 27.3 (21.6–30.8) ml/kg/min; age-adjusted $p = 0.62$; Fig. 1a). A further reduction in peak VO_2 was documented in patients with normal CFVR (median (IQR) 21.8 (18.5–25.4) ml/kg/min; age-adjusted $p = 0.036$). The lowest peak VO_2 values were observed in patients with CMD where median (IQR) peak VO_2 was 17.3 (15.5–21.3) ml/kg/min (age-adjusted $p = 0.001$). The difference remained significant after further adjustment for cardiovascular risk factors ($p = 0.041$).

5.3. Other CPET-derived variables

Percent-predicted peak O_2 pulse was on average 15% lower in patients with CMD compared with controls with normal CFVR (age-adjusted $p = 0.033$; Table 2), while ΔVO2/Δwork rate slope was comparable across the groups (all $p \geq 0.27$). For all participants, no flattening or downsloping in the O_2 pulse and ΔVO2/Δwork rate trajectories were registered.

Peak HR was significantly lower in patients with CMD ($p = 0.031$), resulting in diminished HR reserve compared with controls with normal CFVR (age-adjusted $p < 0.001$; Fig. 1b). This difference remained significant after further adjustment for BMI and cardiovascular risk factors ($p = 0.002$). Thirteen (18%) patients with normal CFVR, 10 (37%) patients with CMD, and only one (5%) control fulfilled criteria for chronotropic incompetence (CI), defined as HR reserve <80% of the predicted value (Appendix, Fig. 2b). HR recovery after 1 and 2 min was significantly reduced in patients with CMD (age-adjusted $p = 0.043$ and $p = 0.008$, respectively; Table 2).

6. Discussion

In the present study, we demonstrated that symptomatic women with CMD and no obstructive CAD have severely reduced exercise

Table 1
Participant characteristics.

	Controls	Controls	Patients	Patients	*p*-Value
	CFVR ≥2	CFVR<2	CFVR ≥2	CFVR<2	
	$n = 22$	$n = 5$	$n = 71$	$n = 27$	
Risk factors					
Age (years)	57 ± 9	61 ± 12	59 ± 10	64 ± 10	0.042
BMI (kg/m^2)	25 (23–27)	27 (21–27)	25 (23–28)	26 (23−31)	0.23
Hypertension[a]	4 (18)	1 (20)	38 (54)	21 (78)	0.002
Hypercholesterolemia[b]	3 (14)	1 (20)	34 (48)	18 (67)	0.002
Diabetes[c]	1 (5)	0	3 (4)	0	0.70
Smoking[d]	9 (41)	3 (60)	37 (52)	15 (56)	0.73
Family history of ischemic heart disease	9 (41)	4 (80)	50 (70)	10 (37)	0.004
Physical activity					
MET - minutes per week	2586 (1413–3999)	1126 (766–2786)	2793 (1209–4914)	1386 (693–3897)	0.72
Functional test <6 months prior to study inclusion					
Myocardial perfusion imaging and/or stress ECG					
Positive	–	–	4 (6)	1 (4)	
Negative	–	–	4 (6)	2 (7)	0.37
Inconclusive	–	–	7 (10)	0	

Data presented as mean ± SD, median (IQR) or number (%). *p*-Value from linear regression model or Chi-square test. Body Mass Index (BMI); metabolic equivalent minutes (MET); transthoracic Doppler echocardiography (TTDE).

[a] Patients diagnosed with hypertension or receiving antihypertensive medication.
[b] Patients diagnosed with hypercholesterolemia or receiving treatment with lipid lowering medication.
[c] Patients diagnosed with diabetes type II.
[d] Current or previous history of smoking.

Table 2
Exercise outcomes in patients and controls.

	Controls	Controls	*p*-Value	Patients	*p*-Value	Patients	*p*-Value
	CFVR ≥2	CFVR<2		CFVR ≥2		CFVR<2	
	$n = 22$	$n = 5$		$n = 71$		$n = 27$	
Resting values							
Mean heart rate, bpm	76 (71–83)	79 (71–87)	0.44	74 (68–83)	0.90	77 (69–87)	0.15
Systolic blood pressure, mmHg	123 (115–140)	127 (120–140)	0.88	133 (121–145)	0.09	134 (129–148)	0.043
Test values							
Test duration, minutes:seconds	12:00 (10:15–14:15)	8:45 (7:35–11:15)	0.27	9:45 (78:00–11:30)	0.002	8:15 (6:45–10:15)	<0.001
Maximal workload, W	175 (150–200)	125 (100–150)	0.20	125 (125–150)	0.001	125 (100–150)	<0.001
Peak heart rate, bpm	163 (156–167)	156 (151–156)	0.11	156 (146–165)	0.11	145 (128–163)	0.031
Heart rate reserve, bpm	87 (79–95)	77 (60–84)	0.030	83 (68–91)	0.10	61 (53–83)	<0.001
Percentage of predicted heart rate reserve, %	101 (93–106)	91 (86–98)	0.09	95 (83–107)	0.18	87 (71–106)	0.028
Peak systolic blood pressure, mmHg	207 (186–220)	218 (206–244)	0.50	209 (190–222)	0.60	214 (187–230)	0.59
Peak minute ventilation, L/min	77 (62–90)	59 (58–62)	0.18	66 (57–78)	0.21	59 (49–70)	0.15
Peak VO_2, ml/kg/min	27.3 (21.6–30.8)	24.2 (20.3–25.1)	0.62	21.8 (18.5–25.4)	0.036	17.3 (15.5–21.3)	0.001
Percentage of predicted peak VO_2, %	123 ± 26	117 ± 22	0.61	112 ± 24	0.069	103 ± 18	0.002
Peak respiratory exchange ratio	1.21 (1.16–1.29)	1.23 (1.16–1.27)	0.85	1.24 (1.20–1.31)	0.39	1.22 (1.17–1.27)	0.99
Ventilatory anaerobic threshold, % of peak VO_2	64 ± 12	67 ± 14	0.73	65 ± 12	0.70	70 ± 12	0.21
Peak O_2 pulse, ml/bpm	11.9 (9.5–13.9)	9.6 (9.2–12.1)	0.74	10.6 (9.1–12.4)	0.33	9.9 (8.5–11.9)	0.18
Percentage of predicted peak O2 pulse, %	130 ± 28	127 ± 20	0.82	125 ± 28	0.45	115 ± 19	0.03
$\Delta VO_2/\Delta$work rate slope, ml/min/W	9.5 (8.7–10.2)	9.2 (8.3–10.0)	0.94	9.2 (8.3–10.0)	1.0	8.6 (7.8–9.8)	0.27
Recovery							
Heart rate recovery at 1 min	29 (25–36)	26 (21–40)	0.99	28 (22–36)	0.81	22 (15–33)	0.043
Heart rate recovery at 2 min	48 (37–53)	46 (30–54)	0.94	42 (35–52)	0.49	32 (27–48)	0.008
ECG changes during test							
Upslope ST-depressions	0	0	–	3 (3)	0.33	0	–
Horizontal or downslope ST-depressions	0	1 (20)	0.033	5 (7)	0.20	2 (7)	0.19

Data presented as median (IQR), mean ± SD or number (%). Controls with CFVR ≥2 used as the reference group when calculating *p*-value. *p*-Values for test parameters (excl. predicted parameters) from age-adjusted linear regression analyses. *p*-Values for predicted parameters from two-sample *t*-test or Wilcoxon rank sum test. *p*-Value for ECG changes from Chi-square test. Watt (W).

capacity compared with sex-matched controls, independent of age and cardiovascular risk factors. Moreover, a combination of angina and CMD was associated with diminished HR reserve and delayed HR recovery.

6.1. Exercise capacity

The average peak VO_2 values for the asymptomatic women with normal CFVR used as the reference group in this study are in line with previously published reference values for healthy women [28]. A few of asymptomatic women enrolled had CFVR <2. Presence of CMD without the symptoms was associated with reduced exercise capacity; however, the reduction was not statistically significant, possibly due to the lack of the statistical power ($n = 5$). We can therefore not comment on whether exercise capacity is affected by CMD in asymptomatic women.

Existing knowledge on exercise performance in symptomatic women with no obstructive CAD is limited to smaller studies describing patients with cardiac syndrome X or exercise intolerance [29,30]. In the current study, presence of angina was associated with reduced peak VO_2; however, the greatest reduction was seen in women with both angina and CMD. Using a cycle ergometry-based CPET with ramp protocol, Chaudhry et al. reported reduced percent-predicted peak VO_2 in a population of women with no obstructive CAD ($n = 49$) compared with healthy sex-matched controls ($n = 59$). It can be speculated, that symptomatic women are more physically restricted and therefore more prone to physical deconditioning. This is not corroborated by the physical activity level assessed using IPAQ, in which weekly MET was comparable between patients and controls. However, IPAQ is validated for ages 18–65 years, which can lead to potential over- or underestimation of the physical activity level in older patients enrolled in the current study. Regardless, exercise capacity in symptomatic women with CMD presented in this study is comparable to patients with coronary heart disease and heart failure [31–34]. Moreover, the average peak VO_2 in symptomatic women with CMD was below the 10th percentile for peak VO_2 in healthy women between the ages of 60 and 69 [28].

6.2. Other CPET-derived variables

We hypothesized that the association between CMD and peak VO_2 could be attributed to cardiac function impairment in the setting of generalized myocardial ischemia; however, we found no echocardiographic evidence of reduced LV function in patients with CMD. Similar results were reported in another study conducted by our group, where Michelsen et al. found reduced LV contractile response, but not LV ejection fraction or diastolic function, in a larger non-overlapping cohort of symptomatic women with CMD [22].

The traditional functional stress testing (e.g. stress ECG, stress echocardiography, and stress myocardial perfusion imaging) have been less effective in detecting patchy myocardial ischemia caused by CMD compared to localized ischemia caused by flow-limiting atherosclerosis [11]. Changes in the CPET-derived O_2 pulse and $\Delta VO_2/\Delta$work rate may be evident before ST segment depression on ECG, wall motion abnormalities, or qualitative myocardial hypoperfusion, thus evaluation of these parameters is recommended in patients suspected for myocardial ischemia undergoing CPET [7]. O_2 pulse reflects stroke volume response to exercise [7]. Exceeding the ischemic work rate threshold can cause stroke volume to decrease, revealing exercise-induced LV dysfunction [7,33,35]. Although diagnostic utility of O_2 pulse in patients with CMD is not clear, the relative reduction in O_2 pulse compared with healthy individuals may confirm subtle ischemic changes not yet detectable by the traditional diagnostic approach. Chaudhry et al. reported percent-predicted peak O_2 pulse to be 6–9% lower in women with angina and no obstructive CAD compared to healthy sex-matched controls [30]. In the current study, percent-predicted peak O_2 pulse was 5% lower in symptomatic patients. Another 10% reduction was related to presence of CMD. Furthermore, different stress stimuli (exercise vs. pharmacological stress) create different oxygen demand during hyperemia, which can potentially explain the detected reduction in O_2 pulse, but not the LV systolic function, in patients with CMD.

The $\Delta VO_2/\Delta$work rate is another indicator of cardiovascular efficiency in patients without limiting factors in oxygen transport capacity.

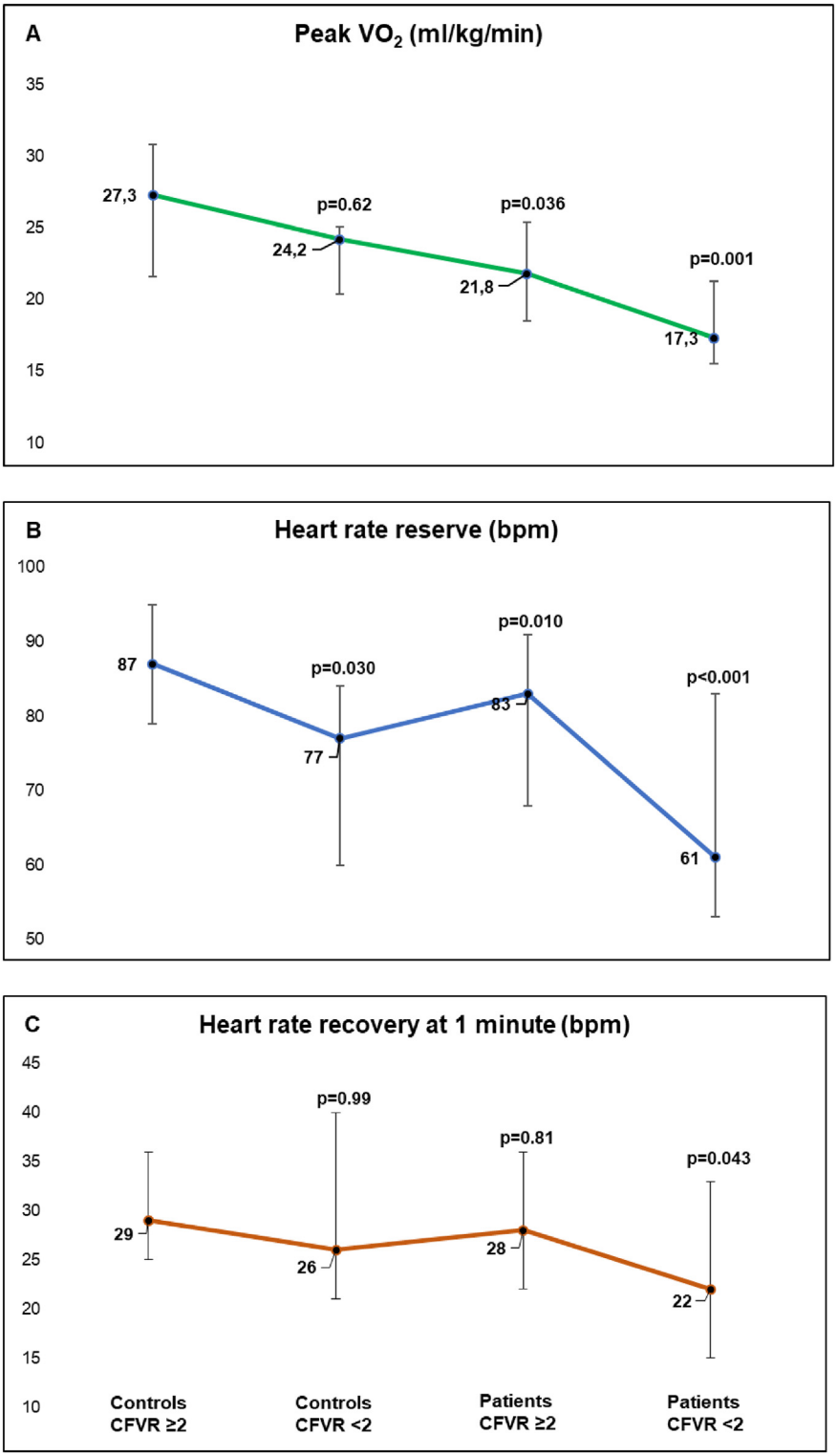


Fig. 1. Median (IQR) peak oxygen uptake (A), heart rate reserve (B), and heart rate recovery at 1 min (C) in controls and patients with and without CMD. *p*-Values from age-adjusted linear regression analyses using controls with CFVR ≥2 as the reference.

In healthy individuals, the increase in the $\Delta VO_2/\Delta$work rate is linear and equals 10.0 ± 1.0 ml/min/W [21]. In patients with reversible myocardial ischemia, the $\Delta VO_2/\Delta$work rate slope is reduced [33]. In the current study, the average $\Delta VO_2/\Delta$work rate slope was significantly below the reference range in patients with CMD.

Reduced HR reserve is common in patients with cardiovascular disease and has shown to be an independent predictor of cardiovascular events [20,36]. In the current study, blunted HR reserve was related to presence of CMD. Furthermore, CI, defined as HR reserve <80% of the predicted value, was revealed in 37% of patients with CMD [20]. The prevalence of CI found in the current CMD population was comparable to the CI prevalence reported in some populations of patients with heart failure (CI between 28% and 43%) [37,38].

A blunted HR recovery at 1 and 2 min post exercise has been associated with unfavorable outcome in general populations and in patients with ischemic heart disease [39,40]. In the current study, blunted HR

recovery was associated with presence of both symptoms and CMD, suggesting a delayed parasympathetic reactivation in these patients [7]. Furthermore, the average HR recovery at 2 min in patients with CMD was <42 bpm, a cut-off associated with all-cause mortality [39].

6.3. Implications of reduced exercise capacity

Persistent angina in the absence of obstructive CAD and impaired coronary microvascular function are both associated with adverse cardiovascular prognosis [5]. Exercise capacity is a significant predictor of cardiovascular disease and death in women [8]. Evidence of poor exercise capacity in symptomatic women with CMD is a novel finding. Prevention of physical deconditioning has shown to limit morbidity, improve quality of life, and lower the risk of cardiovascular events in other patient populations (e.g. heart failure and coronary heart disease) [41,42]. Thus, alongside with pharmacological therapy, exercise-based cardiac rehabilitation, aiming at increasing peak VO_2, may constitute a relevant therapeutic strategy in patients with CMD [11].

It is plausible to assume that exercise intolerance is a contributing factor to the poor quality of life and adverse cardiovascular outcome in symptomatic women with CMD and no obstructive CAD; however, the causal and temporal association between CMD, exercise intolerance and increased cardiovascular morbidity and mortality has yet to be established. Several studies indicate that the inverse association between exercise capacity and risk of cardiovascular events could partially be explained by a less favorable cardiovascular risk profile [8]. In the present study, exercise capacity was significantly lower in patients with CMD, independent of the risk factor profile. Our group has previously reported association between CMD and traditional risk factors in a larger cohort of women enrolled in the iPOWER study [43]. A less favorable cardiovascular risk profile or residual confounding can therefore not be excluded as a potential explanation of the inverse association between exercise capacity, coronary microvascular function and adverse cardiovascular prognosis.

7. Limitations

All participants underwent the same incremental CPET protocol. This resulted in a shorter (<8 min) or longer (>12 min) test phase duration for some participants, due to individual differences in exercise tolerance. Therefore, to ensure test validity all participants with RER <1.1 were excluded. The vasodilator effect of dipyridamole used in the TTDE examination is largely attributed to the non-endothelial dependent pathway; however, some degree of endothelial dependent vasodilation may occur. Thus, the presented associations may be partly contributed to the presence of endothelial dependent CMD. CPET and TTDE were performed within a reasonable time interval (median (IQR) 23 (12–40) days); however, a shorter interval would have been preferable.

8. Conclusions

Women with angina, CMD and no obstructive CAD have markedly impaired exercise capacity compared to asymptomatic women with normal coronary microvascular function. Moreover, presence of CMD is associated with reduced heart rate response and delayed heart rate recovery.

Acknowledgements

We want to thank Departments of Cardiology and Physical- and Occupational Therapy, Hvidovre University Hospital, and Department of Cardiology, Bispebjerg University Hospital for their collaboration on this project. We thank chief physiotherapist Thomas Quaade Bandholm and physiotherapist Anne-Sofie Rendbaek Muusmann for their assistance in data acquisition. Lastly, we want to express our deepest gratitude to the women participating in the iPOWER study for their time and willingness to contribute to the research.

Funding

This work was kindly supported by the Danish Heart Foundation (grant 11-10-R87-B-A3628-22678), Arvid Nilssons Foundation, and Hvidovre Hospital Research Council.

Conflict of interest

The Authors declare that there is no conflict of interest.

Authors' contributions

All co-authors, listed on the title page, have participated in the planning, execution or analysis of the study and resulting manuscript. The submitted version of the manuscript has been read and approved by all co-authors.

Appendix A

Table 3
Comparison of peak VO2 between patient and control groups.

	Controls	Patients	*p*-Value	Patients	*p*-Value
	CFVR ≥2	CFVR ≥2		CFVR<2	
	$n = 26$	$n = 71$		$n = 27$	
Peak VO_2, ml/kg/min	28.6 (22.1–31.7)	21.8 (18.5–25.4)	0.017	17.3 (15.5–21.3)	0.001

Data presented as median (IQR). Controls with CFVR ≥2 used as the reference group when calculating *p*-values from age-adjusted linear regression analyses.

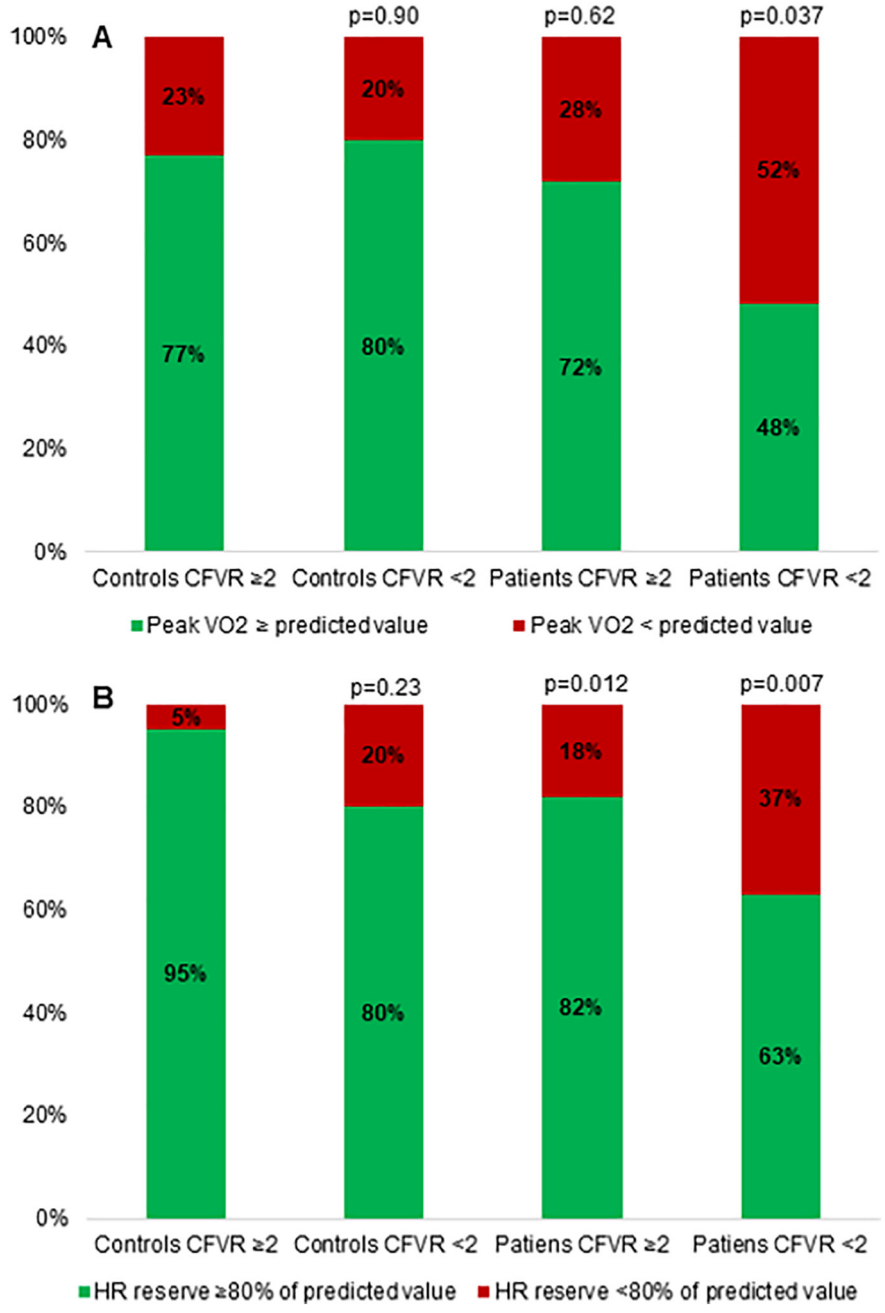
Table 4
Left ventricular systolic and diastolic echocardiographic parameters.

	Controls	Patients	*p*-Value
	CFVR ≥2	CFVR<2	
	$n = 22$	$n = 27$	
Left ventricular diastolic function			
e'	8.60 (7.64–11.26)	9.48 (6.76–11.00)	0.40
E/e' ratio	8.35 (7.10–10.73)	8.34 (6.16–11.05)	0.79
E/A ratio	1.12 (0.99–1.40)	0.99 (0.90–1.13)	0.31
Deceleration time	194 (179–214)	208 (177–230)	0.22

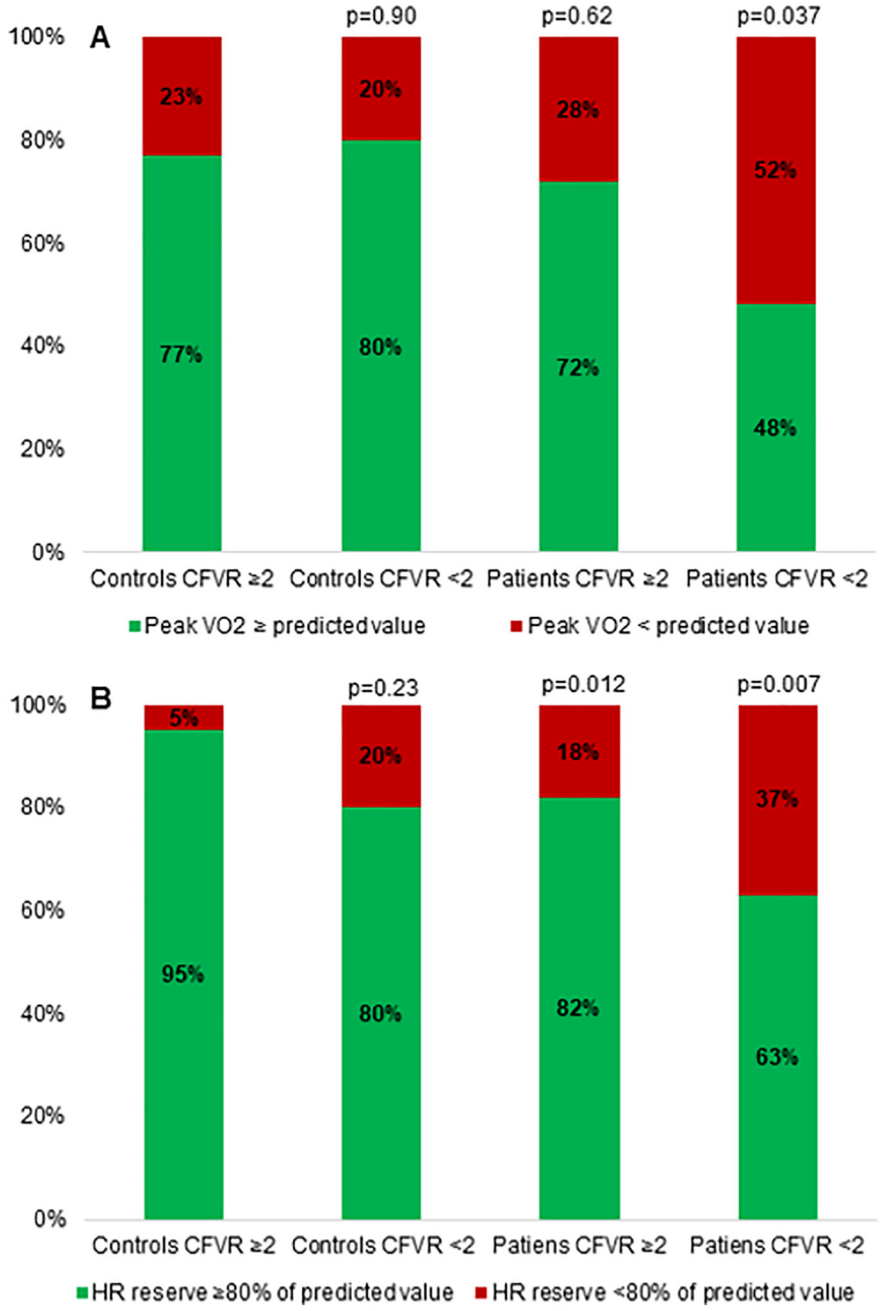
Table 4 (*continued*)

	Controls	Patients	*p*-Value
	CFVR ≥2	CFVR<2	
	n = 22	*n* = 27	
Left ventricular systolic function			
LVEF at rest (%)	54.6 ± 4.7	55.2 ± 5.9	0.98
LVEF at hyperemia (%)	57.7 ± 4.2	59.7 ± 5.7	0.35
Cardiac output at rest (L/min)	4.56 ± 1.0	5.83 ± 1.9	0.011
Cardiac output at hyperemia (L/min)	7.86 ± 1.1	9.16 ± 2.47	0.086

Data presented as median (IQR) or mean ± SD. *p*-Value from age-adjusted linear regression analyses. Left ventricular ejection fraction (LVEF).



Appendix, Fig. 2. Participants categorized by A) peak VO_2 above or below the predicted value; and B) heart rate (HR) reserve above or below 80% of the predicted value. *p*-Values from Chi-square tests using controls with CFVR ≥2 as the reference.



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